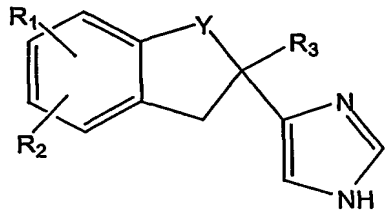
OROMUCOSAL FORMULATION AND PROCESS FOR PREPARING THE SAME

FIELD OF THE INVENTION

The present invention relates to an oromucosal formulation comprising as an active ingredient a substituted imidazole derivative of formula (I)



(I)

wherein Y is $-CH_2-$ or -CO-, R_1 is halogen or hydroxy, R_2 is H or halogen and R_3 is H or lower alkyl, or an acid addition salt thereof.

The invention also relates to a process for preparing the oromucosal formulation in question.

BACKGROUND OF THE INVENTION

The compounds of the above-mentioned formula (I) are highly selective and long-acting antagonists of α_2-adrenoceptors. The compounds are especially valuable in the treatment of cognitive disorders. Compounds of formula (I) and their preparation have been described in patent publication EP 0 618 906 B1. Specific examples of such compounds are 4-(2-ethyl-5-fluoroindan-2-yl)-1*H*-imidazole, i.e. fipamezole, and 4-(5-fluoroindan-2-yl)-1*H*-imidazole.

Although the compounds of formula (I) and their salts have good properties as such, they have disadvantages, when formulated for conventional oral administration, i.e. the normal route for administering said compounds. A problem is that the compounds rather quickly decompose in the gastrointestinal area or other body systems prior to accessing systemic blood flow and the therapeutic target organs. This in turn significantly lowers the effect of the compounds in question.

Toxicology studies carried out with dogs (see Example 8) have further suggested that cardiac safety considerations are of importance

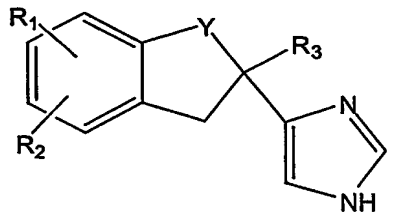
whereas QT prolongation was observed with high oral doses of fipamezole when the systemic concentration of fipamezole reached about 2000 ng/ml.

OBJECT AND SUMMARY OF THE INVENTION

One object of the present invention is to provide a formulation for administering compounds of formula (I) safely and efficiently.

Another object of the present invention is to provide a process for preparing the formulation.

Thus, according to one aspect of this invention concerns an oromucosal formulation comprising as an active ingredient a substituted imidazole derivative of formula (I)



(I)

where Y is $-CH_2-$ or $-CO-$, R_1 is halogen or hydroxy, R_2 is H or halogen and R_3 is H or lower alkyl, or an acid addition salt thereof, together with additives conventionally used in oromucosal formulations.

According to another aspect, the invention concerns a process for preparing the oromucosal formulation.

DETAILED DESCRIPTION OF THE INVENTION

It has now surprisingly been found that the problems of quick decomposition in the gastrointestinal area and compromised cardiac safety of the compounds of formula (I) can be alleviated by formulating the compounds of formula (I) into oromucosal formulations. Such formulations are effective and easy to handle, and therefore they have an advantage in terms of practical administration to the patient.

Suitable additives to be used in the formulation according to the present invention are adjuvants, expedients etc. including solvents, preserving agents, flavouring agents, fillers, gelling agents and mucoadhesive polymers. Preferred solvents are alcohols, especially ethanol, water and mixtures thereof. Preferred preserving agents are lower alkyl parahydroxybenzoates, especially methyl and propyl parahydroxybenzoate, and mixtures thereof. Preferred

flavouring agents are aspartame, artificial flavours, such as black currant 502.009, and mixtures thereof.

In this context, the oromucosal formulation means any type of formulation administered via oral mucosa. Such formulations include e.g. sprays, gels, mucoadhesive buccal tablets and pastes, sublingual tablets and like. The formulation is preferably in the form of a spray.

In this context, the term *halogen* refers to F, Cl, Br and I, preferably to F and Cl and most preferably to F.

In this context, the term *lower alkyl* refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms and most preferably 1 or 2 carbon atoms.

In this context, the term *an acid addition salt* refers to an addition salt of any pharmaceutically acceptable acid, preferably hydrochloric acid.

In this context, the term *an additive conventionally used in oromucosal formulations* refers to any additive known by the person skilled in the art to be applicable for oromucosal formulations.

An especially preferred active ingredient is fipamezole (JP-1730, 4-(2-ethyl-5-fluoroindan-2yl)-1*H*-imidazole hydrochloride). A formulation containing said preferred active ingredient is prepared according to the invention by mixing and dissolving ethanol (96%), purified water, methylparahydroxybenzoate, propylparahydroxybenzoate and aspartame at room temperature, at +15 to +25 °C. Followed by adding and dissolving 4-(2-ethyl-5-fluoroindan-2-yl)-1H-imidazole and artificial flavour, such as black currant 502.009A, at room temperature, at +15 to +25 °C. The volume of the mixture is adjusted with purified water, followed by filtering and the desired spray formulation is recovered.

The following examples illustrate the invention, but are not intended to restrict the scope of the invention.

Example 1

Spray formulation containing 4-(2-ethyl-5-fluoroindan-2-yl)-1*H*-imidazole hydrochloride (fipamezole)

Fipamezole oromucosal spray

Ingredient	Quantity per 1 ml	Function
Fipamezole	15.0 mg	Active
Methyl parahydroxybenzoate	1.8 mg	Preservative
Propyl parahydroxybenzoate	0.2 mg	Preservative
Aspartame	0.5 mg	Flavouring agent
Artificial flavour*	0.4 mg	Flavouring agent
Ethanol (96 %)	0.416 ml	Solvent
Purified water	ad 1.0 ml	Solvent

*Artificial flavour, such as black currant 502.009A, for example, but not restricted to.

Example 2

Spray formulation containing 4-(2-ethyl-5-fluoroindan-2-yl)-1*H*-imidazole hydrochloride (fipamezole)

Fipamezole oromucosal spray

Ingredient	Quantity per 1 ml	Function
Fipamezole	161.0 mg	Active
Methyl parahydroxybenzoate	1.8 mg	Preservative
Propyl parahydroxybenzoate	0.2 mg	Preservative
Aspartame	0.5 mg	Flavouring agent
Artificial flavour*	0.4 mg	Flavouring agent
Ethanol (96 %)	0.416 ml	Solvent
Purified water	ad 1.0 ml	Solvent

*Artificial flavour, such as black currant 502.009A, for example, but not restricted to.

Example 3

Preparation of a spray formulation containing 4-(2-ethyl-5-fluoroindan-2-yl)-1*H*-imidazole hydrochloride (fipamezole)

416.0 ml of ethanol (96 %) was mixed with 450.0 ml of purified water to form a homogenous mixture. 1.80 g of methylparahydroxybenzoate, 0.20 g of propylparahydroxybenzoate and 0.5 g of aspartame were added to the mixture and dissolved at room temperature, at +15 to +25 °C. 15.0 g of fipamezole, 0.4 g of black currant flavour were added to the mixture and dissolved at room temperature, at +15 to +25 °C. The volume of the mixture was adjusted to 1000.0 ml with purified water. The solution was filtered and the desired spray formulation was recovered.

Example 4

Preparation of an oromucosal gel formulation containing 4-(2-ethyl-5-fluoroindan-2-yl)-1*H*-imidazole hydrochloride (fipamezole) 30 mg

Composition

Ingredient		Amount/single dose
1	Fipamezole	30 mg
2	Ethanol (96 %)	250 mg
3	Poloxamer 407	200 mg
4	Liquid flavour (artificial)	0.5 mg
5	Aspartame (sweetener)	0.5 mg
6	Purified water	519 mg
	Total of	1000 mg

Method of preparation

Fipamezole (1) and ethanol (96 %) (2) are mixed and dissolved to form a solution A. Purified water (6), poloxamer 407 (3), liquid flavour (4), and aspartame (5) are mixed and dissolved to form a solution B. Solution A and

solution B are cooled down to approx. +5 °C, and mixed together to form a homogenous solution. Oromucosal gel formulation is recovered.

Example 5

Preparation of a mucoadhesive buccal tablet formulation containing 4-(2-ethyl-5-fluoroindan-2-yl)-1*H*-imidazole hydrochloride (fipamezole) 30 mg

Composition

	Ingredient	Amount/single dose
1	Fipamezole	30 mg
2	Carbomer 934P	12.35 mg
3	Hydroxypropylmethylcellulose	49.4 mg
4	Flavour (artificial)	4 mg
5	Aspartame (sweetener)	4 mg
6	Magnesium stearate	0.25 mg
	Total of	100 mg

Method of preparation

Fipamezole (1), carbomer 934P (2), hydroxypropylmethyl-cellulose (3), flavour (4), aspartame (5), and magnesium stearate (6) are mixed to form a homogenous mixture. The mixture is compressed to tablets of a suitable size. Mucoadhesive buccal tablets are recovered.

Example 6

Preparation of a sublingual tablet formulation containing 4-(2-ethyl-5-fluoroindan-2-yl)-1*H*-imidazole hydrochloride (fipamezole) 30 mg

Composition

	Ingredient	Amount/single dose
1	Fipamezole	30 mg
2	Lactose monohydrate	30 mg
3	Povidone	2.4 mg
4	Microcrystalline cellulose	10.8 mg
5	Flavour	3.2 mg
6	Aspartame (sweetener)	3.2 mg
7	Magnesium stearate	0.4 mg
	Total of	80 mg

Method of preparation

Fipamezole (1), lactose monohydrate (2), flavour (5), and aspartame (6) are mixed to form a homogenous mixture. The mixture is granulated with 10 % aqueous solution of povidone (3). Granules are formed in either high-shear or low-shear mixer. Granulated mixture is let to dry. Dry, granulated mixture is passed through a screen to obtain freely flowing granulate. Microcrystalline cellulose (4) and magnesium stearate (7) are mixed with the granulate. The final blend is compressed to tablets of a suitable size. Sublingual tablets are recovered.

Example 7

Oromucosal delivery of fipamezole

Plasma levels of fipamezole were studied in healthy male volunteers after oral administration of the drug as a solution. Blood samples for pharmcokinetic evaluation were collected for 24 hours after the drug

administration. The concentration of fipamezole in plasma was measured with HPLC-MS/MS, and the pharmacokinetic parameters were calculated. The pharmacokinetics of fipamezole was evaluated with TopFit 2.0 pharmacokinetic program. The C_{max} and t_{max} values were read from the concentration vs. time curves, and the apparent elimination phase half-lives from the terminal part of the semilogarithmic concentration vs. time curve (see Figure 1). AUC values were calculated both to infinity and up to the last collection time with quantifiable fipamezole concentration. The results are given in Table 1.

Table 1. Mean (SD) pharmacokinetic parameters of fipamezole at the dose level of 30 mg. t_{max} values are given as median and range.

30-mg dosing	C_{max} (ng/ml)	t_{max} (h)a	$t_{1/2el}$ (h)	AUC_{0-inf} (ng*h/ml)
Oral	1.59 (0.38)	1.0 (0.75-2.0)	3.10 (2.23)	7.65 (2.99)
Oromucosal, tablet	31.74 (13.50)	0.85 (0.43)	3.10 (1.00)	115.6 (41.10)
Oromucosal, spray	49.2 (11.0)	0.7 (0.5-1.0)	2.10 (0.20)	157.1 (24.7)

C_{max}, maximal drug concentration in serum; t_{max}, time of maximal drug concentration in serum; $t_{1/2el}$, apparent elimination phase half-life; AUC_{0-inf}, area under the drug concentration in serum *vs.* time curve from time 0 to infinity.

Mean plasma concentration time plot following single dose administration of 30 mg fipamezole via an oral, oromucosal spray and an oromucosal tablet on a semilogarithmic scale is shown in Figure 1.

Example 8

Cardiac safety

Cardiac safety was studied in dogs in a 30-day dog toxicology study using oral dosing and dog toxicology studies using buccal dosing.

In the 30-day dog toxicology study fipamezole was administered orally at doses of 1, 5, 10 and 15 mg/kg/day for 30 days, resulting in maximum systemic fipamezole concentrations of about 200, 1000, 2000 and 3300 ng/ml, respectively. These in vivo results in the dog suggested that QT prolongation was observed when the systemic concentration of fipamezole reached about 2000 ng/ml.

In another toxicology study four male dogs were given fipamezole in buccal spray doses of 1, 5 and 10 mg/kg in a sequential dosing regimen with 5 to 15 days between doses. Blood pressure (systolic, diastolic and mean), heart rate and ECGs were monitored before and up to 12 hours after dosing. At 30 minutes after dosing with 5 and 10 mg/kg significant transient increases in absolute values for blood pressure and heart rate were observed. No ECG changes (P wave amplitude, P wave duration, P-Q interval, QRS interval or Q-T [Q-Tcv, QTc] interval) were apparent after fipamezole dosing at each dose level.

Yet another toxicology study using buccal delivery to dogs at dose levels of 1, 5 and 10 mg/kg/day for up to 4 weeks showed no apparent changes in ECG. Maximum systemic concentrations of fipamezole after dosing on the first day of this study were about 800, 2000 and 3300 ng/ml.